

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
16 June 2005 (16.06.2005)

PCT

(10) International Publication Number  
**WO 2005/054517 A3**

(51) International Patent Classification:  
**C12Q 1/68** (2006.01)

(74) Agents: DAVISON, Barry, L. et al; 2600 Century Square, 1501 Fourth Avenue, Seattle, Wa 98101-1688 (US).

(21) International Application Number:  
PCT/US2004/040289

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FT, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

(22) International Filing Date:  
1 December 2004 (01.12.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:  
03090414.8 1 December 2003 (01.12.2003) EP  
04090040.9 10 February 2004 (10.02.2004) EP  
04090187.8 10 May 2004 (10.05.2004) EP  
04090292.6 21 July 2004 (21.07.2004) EP

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

(71) Applicant (for all designated States except US): **EPIGENOMICS AG** [DE/US]; Kleine Praesidentenstrasse 1, 10178 Berlin (DE).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **DAY, Kevin, J.** [US/US]; 27954 251st Avenue SE, Maple Valley, WA 98038 (US). **COTTRELL, Susan** [US/US]; 3509 Meridian Avenue N, Seattle, WA 98103 (US). **DISTLER, Jürgen** [OE/DE]; Hewaldstr. 2, 10825 Berlin (DE). **MOROTTI, Andrew** [US/US]; 316 Bellevue Avenue E., #402, Seattle, WA 98102 (US). **YAMAMURA, Su** [KR/US]; 15349 SE 42nd Street, Bellevue, WA 98006 (US). **DEKKER, Sharon** [US/US]; 23306 SE 209th Place, Maple Valley, WA 98038 (US). **OCAMP, Yreka** [US/US]; 13520 Linden Avenue N, Apt. 425, Seattle, WA 98133 (US). **DEVOS, Theo** [CA/US]; 1208 NE 100th Street, Seattle, WA 98125 (US).

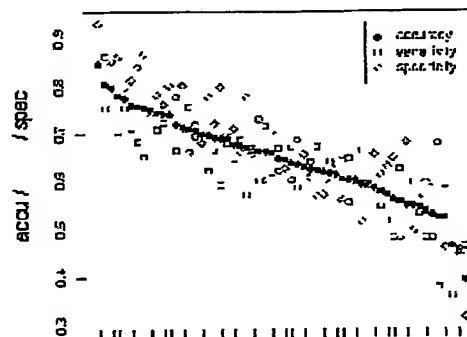
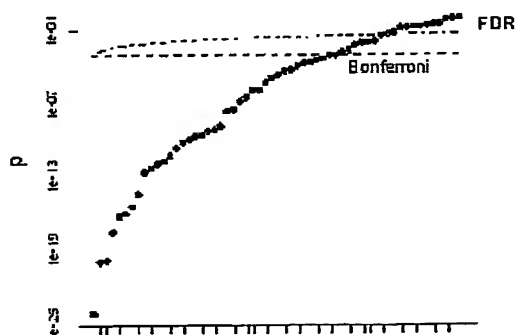
**Published:**

- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

(88) Date of publication of the international search report:  
16 February 2006

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: METHODS AND NUCLEIC ACIDS FOR THE ANALYSIS OF GENE EXPRESSION ASSOCIATED WITH THE DEVELOPMENT OF PROSTATE CELL PROLIFERATIVE DISORDERS



(57) Abstract: The following application provides methods and nucleic acids for the detection of and/or differentiation between prostate cell proliferative disorders. This is achieved by the analysis of the expression status of a panel of genes, or subsets thereof.

WO 2005/054517 A3

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US2004/040289

A. CLASSIFICATION OF SUBJECT MATTER C12Q1/68		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED		
Minimum documentation searched (classification system followed by classification symbols) C12Q		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practical, search terms used) EPO-Internal , WPI Data, PAJ, BIOSIS, EMBASE, Sequence Search		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
X	WO 02/103042 A (EPIGENOMICS AG) 27 December 2002 (2002-12-27) sequences 9, 26	1-32
X	WO 02/103041 A (EPIGENOMICS AG; DISTLER, JUERGEN; MODEL, FABIAN; ADORJAN, PETER) 27 December 2002 (2002-12-27) sequences 17, 51	1-32
X	WO 02/18632 A (EPIGENOMICS AG; OLEK, ALEXANDER; PIEPENBROCK, CHRISTIAN; BERLIN, KURT;) 7 March 2002 (2002-03-07) sequences 29229, 29230, 29231	38-47
X	WO 02/00926 A (EPIGENOMICS AG; OLEK, ALEXANDER; PIEPENBROCK, CHRISTIAN; BERLIN, KURT) 3 January 2002 (2002-01-03) sequences SEQ ID NO 111, 177, 258	38-47
- / - -		
<input checked="" type="checkbox"/> Further documents are listed in the continuation of box C <input checked="" type="checkbox"/> Patent family members are listed in annex		
* Special categories of cited documents 'A' document defining the general state of the art which is not considered to be of particular relevance 'E' earlier document but published on or after the international filing date 'L' document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) 'O' document referring to an oral disclosure, use, exhibition or other means 'P' document published prior to the international filing date but later than the priority date claimed 'T' later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention 'X' document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone 'Y' document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art '&' document member of the same patent family		
Date of the actual completion of the international search  3 August 2005		Date of mailing of the international search report  20. 12. 2005
Name and mailing address of the ISA European Patent Office P B 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel (+31-70) 340-2040, Tx 31 651 epo nl, Fax (+31-70) 340-3016		Authorized officer  Guarinos Vinals, E

## INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US2004/040289

C(Communication) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
X	wo 01/76451 A (EPIGENOMICS AG; OLEK, ALEXANDER; PIEPENBROCK, CHRISTIAN; BERLIN, KURT) 18 October 2001 (2001-10-18) sequence 27	38-47
X	----- DATABASE EMBL human genomic sequence 30 April 2002 (2002-04-30), XP002338678 Database accession no. AC063960 abstract	38-44
X	----- DATABASE EMBL human EST 22 December 1999 (1999-12-22), XP002338679 Database accession no. AI702131 abstract	38,42-44
X	----- DATABASE EMBL human EST 24 May 2000 (2000-05-24), XP002338680 Database accession no. AW853489 abstract	38-41
X	----- DATABASE EMBL human EST 1 December 2000 (2000-12-01), XP002338681 Database accession no. BF432721 abstract	38-41
X	----- DATABASE EMBL human EST 22 March 2003 (2003-03-22), XP002338682 Database accession no. BX374481 abstract	38-41
A	----- YAMADA YASUSHI ET AL: "Aberrant methylation of the vascular endothelial growth factor receptor-1 gene in prostate cancer." CANCER SCIENCE, vol. 94, no. 6, June 2003 (2003-06), pages 536-539, XP002338911 ISSN: 1347-9032	
A	----- wo 02/081749 A (UNIVERSITY OF SOUTHERN CALIFORNIA; MARKL, ISABEL; JONES, PETER, A; TOM) 17 October 2002 (2002-10-17)	
A	----- wo 99/55905 A (COMMONWEALTH SCIENTIFIC AND INDUSTRIAL RESEARCH ORGANISATION; CLARK, S) 4 November 1999 (1999-11-04)	
A	----- wo 03/044232 A (THE JOHNS HOPKINS UNIVERSITY SCHOOL OF MEDICINE; SIDRANSKY, DAVID) 30 May 2003 (2003-05-30)	

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US2004/040289

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
wo 02103042 A	27-12-2002	CA 2445731 A1	27-12-2002
		DE 10128508 A1	06-02-2003
		EP 1395686 A2	10-03-2004
		OP 2004529661 T	30-09-2004
		US 2003113750 A1	19-06-2003
wo 02103041 A	27-12-2002	DE 10128509 A1	02-01-2003
		EP 1395685 A2	10-03-2004
		US 2004219549 A1	04-11-2004
wo 0218632 A	07-03-2002	AU 1218802 A	13-03-2002
		CA 2420840 A1	27-02-2003
		EP 1423528 A2	02-06-2004
		JP 2004516821 T	10-06-2004
		MX PA03001834 A	01-08-2003
		US 2004234960 A1	25-11-2004
wo 0200926 A	03-01-2002	AU 7637101 A	14-01-2002
		AU 7752101 A	14-01-2002
		AU 7970701 A	14-01-2002
		AU 8391501 A	08-01-2002
		AU 8391601 A	14-01-2002
		AU 8757501 A	08-01-2002
		AU 8757601 A	08-01-2002
		AU 8961701 A	08-01-2002
		WO 0202806 A2	10-01-2002
		WO 0202807 A2	10-01-2002
		WO 0200927 A2	03-01-2002
		WO 0200928 A2	03-01-2002
		WO 0202808 A2	10-01-2002
		WO 0200705 A2	03-01-2002
		WO 0202809 A2	10-01-2002
		EP 1294947 A2	26-03-2003
		EP 1297182 A2	02-04-2003
		EP 1294948 A2	26-03-2003
		EP 1294950 A2	26-03-2003
		EP 1356099 A2	29-10-2003
		EP 1294951 A2	26-03-2003
		EP 1355932 A2	29-10-2003
		EP 1297185 A2	02-04-2003
		JP 2004501666 T	22-01-2004
		US 2004023230 A1	05-02-2004
		US 2003143606 A1	31-07-2003
		US 2004115630 A1	17-06-2004
wo 0176451 A	18-10-2001	AU 5478801 A	23-10-2001
		AU 5479401 A	23-10-2001
		AU 7566301 A	23-10-2001
		AU 7633001 A	23-10-2001
		AU 7633101 A	23-10-2001
		AU 7748701 A	23-10-2001
		AU 7842001 A	07-11-2001
		AU 8960001 A	11-12-2001
		WO 0177375 A2	18-10-2001
		WO 0177164 A2	18-10-2001
		WO 0177376 A2	18-10-2001
		WO 0177377 A2	18-10-2001
		WO 0181622 A2	01-11-2001

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US2004/040289

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
wo 0176451	A	wo 0192565 A2	06-12-2001
		wo 0177378 A2	18-10-2001
		EP 1268857 A2	02-01-2003
		EP 1272670 A2	08-01-2003
		EP 1278893 A2	29-01-2003
		EP 1274865 A2	15-01-2003
		EP 1274866 A2	15-01-2003
		EP 1360319 A2	12-11-2003
		EP 1370685 A2	17-12-2003
		EP 1268861 A2	02-01-2003
		JP 2004508807 T	25-03-2004
		JP 2003534780 T	25-11-2003
		JP 2003531589 T	28-10-2003
		US 2003082609 A1	01-05-2003
		US 2003162194 A1	28-08-2003
		US 2003148326 A1	07-08-2003
		US 2004067491 A1	08-04-2004
		US 2003148327 A1	07-08-2003
		US 2004076956 A1	22-04-2004
wo 02081749	A	EP 1360317 A2	12-11-2003
	17-10-2002	JP 2004527245 T	09-09-2004
wo 9955905	A	CA 2326494 A1	04-11-1999
	04-11-1999	EP 1071815 A1	31-01-2001
		JP 3522690 B2	26-04-2004
		JP 2002512810 T	08-05-2002
		NZ 507987 A	27-02-2004
		ZA 200006803 A	10-05-2001
wo 03044232	A	AU 2002352745 A1	10-06-2003
	30-05-2003	CA 2467455 A1	30-05-2003
		EP 1456413 A1	15-09-2004
		JP 2005509445 T	14-04-2005

# INTERNATIONAL SEARCH REPORT

International application No  
PCT/US2004/040289

## Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons.

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely  
see FURTHER INFORMATION sheet PCT/ISA/210
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out specifically
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows.

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers the invention first mentioned in the claims, it is covered by claims Nos. :  
2 (completely), 1,4, 5-47 (partially)
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims, it is covered by claims Nos. :

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest

☐ No protest accompanied the payment of additional search fees

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.I

Although claims 5, 14, 33 (that explicitly comprise the step of obtaining from a subject a biological sample) and claim 47 (as far as an "in vivo" method is concerned) are directed to a diagnostic method practised on the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

Invention 1: claim 2 completely and claims 1, 4, 5-47 partially

A method for the detection of and/or differentiation between prostate cell proliferative disorders in a subject comprising contacting genomic DNA isolated from a biological sample obtained from the subject, with at least one reagent, or series of reagents that distinguishes between methylated and non-methylated CpG dinucleotides within one or a combination of target nucleic acids, each of said target nucleic acids comprising essentially of all or part of the sequence of the gene or the genomic sequence SEQ ID NO: 1023, a method for detecting and/or distinguishing between or among prostate cell proliferative disorders in a subject wherein the target sequence comprises, or hybridizes under stringent conditions to at least 16 contiguous nucleotides of a sequence taken from the group consisting of SEQ ID NO: 1023, a method for detecting and/or distinguishing between or among prostate cell proliferative disorders in a subject wherein distinguishing between methylated and non-methylated CpG dinucleotide sequences within the target sequence (s) comprises methylation state- dependent conversion or non-conversion of at least one CpG dinucleotide sequence to the corresponding converted or non-converted dinucleotide sequence within a sequence selected from the group consisting of SEQ ID NO: 1041 and 1042, a method for detecting and/or distinguishing between or among prostate cell proliferative disorders in a subject comprising, in each case a contiguous sequence at least 9 nucleotides in length that is complementary to or hybridizes under moderately stringent or stringent conditions to a sequence selected from the group consisting of SEQ ID NO: 1041 and 1042, a treated nucleic acid derived from SEQ ID NO: 1023, a nucleic acid comprising at least 16 contiguous nucleotides of a treated genomic DNA sequence selected from the group consisting of SEQ ID NOS: 1041, 1042, 1065 and 1066, an oligomer comprising a sequence of at least 9 contiguous nucleotides that is complementary to or hybridizes under moderately stringent or stringent conditions to a treated genomic DNA sequence selected from the group consisting of SEQ ID NO: 1023, a kit comprising bisulfite reagent and an oligomer comprising a sequence of at least 9 contiguous nucleotides that is complementary to or hybridizes under moderately stringent or stringent conditions to a treated genomic DNA sequence selected from the group consisting of SEQ ID NO: 1041, 1042, 1065 and 1066.

---

Inventions 2-17: claims 1, 3-47 partially



## FURTHER INFORMATION CONTINUED FROM POT/ISA/ 210

Inventions 2-17: the same as Invention 1 but relating to SEQ ID NO:57 (GSTP1), SEQ ID NO:20 (PROSTAGLANDIN E2 RECEPTOR), SEQ ID NO:36 (HISTONE H4), SEQ ID NO:1171 (RASSF1A), SEQ ID NO:51 (PR-DOMAIN ZINC FINGER PROTEIN 16), SEQ ID NO:31 (LIM DOMAIN KINASE 1), SEQ ID NO:24 (ORPHAN NUCLEAR RECEPTOR NR5A2), SEQ ID NO:11, SEQ ID NO:1028, SEQ ID NO:4 (LIM/HOMEOBOX PROTEIN LHX9), SEQ ID NO:1116, SEQ ID NO:1025, SEQ ID NO:1020, SEQ ID NO:18 (LYSOSOMAL-ASSOCIATED MULTITRANSMEMBRANE PROTEIN), SEQ ID NO:1019 and SEQ ID NO:1027 and their respective related sequences as disclosed in Table 26, pages 140-142 of the description.

---

Invention 18: claims 38-47 partially

A treated nucleic acid derived from SEQ ID NO: 1, a nucleic acid comprising at least 16 contiguous nucleotides of a treated genomic DNA sequence selected from the group consisting of SEQ ID NOS: 60, 61, 178 and 179, an oligomer comprising a sequence of at least 9 contiguous nucleotides that is complementary to or hybridizes under moderately stringent or stringent conditions to a treated genomic DNA sequence of SEQ ID NO: 1, a kit comprising at least one nucleic acid molecule or peptide nucleic acid molecule comprising a contiguous sequence of at least 9 nucleotides that is complementary to or hybridizes under moderately stringent or stringent conditions to a sequence selected from the group consisting of SEQ ID NOS: 60, 61, 178 and 179, their use for the detection of and/or differentiation between or among prostate cell proliferative disorders.

---

Inventions 19-73: claims 38-47 partially

Inventions 19-73: the same as Invention 18 but relating to SEQ ID NOS: 2, 3, 5-10, 12-17, 19, 21-23, 25-30, 32-35, 37-50, 52-56, 58-1018, 1021, 1022, 1024, 1026 and their respective related sequences as disclosed in Table 26, pages 140-142 of the description.

---